

Endocrine and Metabolic Agents : Metabolic Modifiers – X-Linked Hypohosphatemia (XLH) Agents burosumab-twza (Crysvita®)

Medical policy no. 30.90.95-1

Effective Date: July 1, 2019

Background:

X-linked hypophosphatemia (XLH) is an inherited disorder associated with PHEX gene sequence mutation and subsequent inactivity of the PHEX protein. With this mutation, the protein fibroblast growth factor 23 (FGF23) concentration is increased. FGF23 regulates the reabsorption of phosphate in the kidneys, and too much of FGF23 reduces the amount of phosphate reabsorbed by the kidneys leading to hypophosphatemia. The prevalence of X-linked hypophosphatemia is about 1 in 20,000.

Symptoms of X-linked hypophosphatemia can include rickets, bone softening, bone pain, muscle pain, muscle weakness, waddling gait, bowing of legs, other skeletal abnormalities, joint pain due to calcification of tendons and ligaments, short stature, abnormal tooth development, tooth abscesses, dental pain, and hearing loss. Some patients may have no signs or symptoms, and other patients may experience persistent discomfort or complications. Symptoms for many become apparent within first 18 months of life when legs begin to bear weight, but some patients do not develop symptoms until adulthood.

The diagnosis is made based on slow growth rate and bowing of legs or other skeletal abnormalities, low levels of phosphate, high levels of FGF23 in the blood, lack of response of phosphate levels to vitamin D treatment, and/or phosphate wasting in the kidneys. Genetic testing is available and may confirm diagnosis, but is not necessary for diagnosis.

The typical treatment of X-linked hypophosphatemia is phosphate supplements and high-dose calcitriol. Treatment may also include growth hormones, corrective surgery and dental treatment. Unlike other forms of rickets, ingestion of vitamin D is relatively ineffective in x-linked hypophosphatemia. Burosumab-twza is an antibody that restores renal reabsorption of phosphate and increases serum 1, 25 hydroxyvitamin D levels by binding to and inhibiting fibroblast growth factor 23 (FGF23). It is the first FDA-approved treatment indicated for the underlying cause of XLH in patients 1 year of age and older.

Medical necessity:

Drug	Medical Necessity
Burosumab-twza (Crysvita)	<p>Burosumab-twza may be considered medically necessary when used for the diagnosis of X-linked hypophosphatemia (XLH).</p> <p>Burosumab-twza is considered NOT medically necessary when the clinical criteria below is not met OR for all other indications.</p>

Clinical policy:

Drug	Clinical Criteria (Initial Approval)
Burosumab-twza (Crysvita)	<p>Burosumab-twza may be covered when ALL of the following are met:</p> <ol style="list-style-type: none"> 1) Diagnosis of X-linked hypophosphatemia confirmed by <ol style="list-style-type: none"> a) Genetic testing for PHEX-gene mutations OR b) Lab values consistent for the diagnosis of XLH and for ruling out other diagnoses, including all of the following: <ol style="list-style-type: none"> a. Elevated serum FGF23; AND b. Hypophosphatemia; AND c. Normal serum calcium; AND d. Elevated serum alkaline phosphate; AND e. 1, 25 hydroxyvitamin D levels; AND 2) Patient age 1 year or older; AND 3) Serum phosphorus is below normal range for age; AND 4) Patient has not received oral phosphate or active vitamin D analogs in the previous week; AND 5) Patient must have an inadequate response or intolerance to oral phosphate and vitamin D treatment for at least 6 months; AND 6) Patient does not have severe renal impairment, defined as GFR less than 30 mL/min; AND 7) Documentation of clinical signs and/or symptoms of the disease (e.g., rickets, growth retardation, musculoskeletal pain, bone fractures) for patients <u>greater than or equal to</u> 18 years old; AND 8) Prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders. <p>If ALL criteria are met, the request will be approved for 6 months</p>
	<p>Criteria (Reauthorization)</p> <p>Burosumab-twza may be continued when ALL of the following are met:</p> <ol style="list-style-type: none"> 1) Current serum phosphorus level is below the upper limit of lab normal range; AND 2) Positive clinical response to drug defined as: <ol style="list-style-type: none"> a) Increase in serum phosphorus levels; OR b) Improvement in symptoms (e.g. skeletal pain, linear growth, improvement in skeletal deformities, reduction of fractures); OR c) Reduction in serum alkaline phosphatase activity; OR d) Improvement in radiographic imaging of Rickets/osteomalacia; AND 3) Prescribed by or in consultation with a specialist experienced in the treatment of metabolic bone disorders. <p>If ALL criteria are met, the request will be approved for 12 months</p>

Dosage and quantity limits:

Drug Name	Dose and Quantity Limits
Maximum dose	90mg per administration
Dosing Frequency	Adults: 1 subcutaneous injection every 4 weeks Pediatric: 1 subcutaneous injection every 2 weeks

Coding:

HCPCS Code	Description
J0584	Injection, burosumab-twza, 1 mg

Definitions:

Term	Description
Thacher Rickets Severity Score (RSS)	A 10-point score for radiographs of wrists and knees to assess the degree of metaphyseal fraying and cupping and the proportion of growth plate affected. Total points progress in half point increments from 0-10: wrists (0-4) plus knees (0-6) Higher scores indicate a more severe state of rickets, a reduction indicates an improvement in severity.
Radiographic Global Impression of Change (RGI-C)	A 7-point scale (-3= severe worsening; 0=no change; +3= near/complete healing) designed for comprehensive evaluation of skeletal health. RGI-C scores assess changes in the severity of rickets using the disease-specific qualitative RGI-C scoring system. An RGI-C score $\geq +2.0$ indicates substantial healing of rickets.

Evidence review:Adults:

A randomized, double blind, placebo-controlled trial of 24 weeks of treatment was conducted in 134 adults 19-66 years old. Patients were randomized to receive placebo or burosumab-twza 1mg/kg every 4 weeks. An increased normalized serum phosphorous was demonstrated in the treatment group (94%) compared to placebo (8%) through week 24. The number of healed active fractures and pseudofractures at week 24 in the burosumab-twza group was 50% and 41%, compared to 0.5 and 9% in the placebo group.

An open-label, single-arm study was conducted in 14 adults age 25-52. The primary endpoint of the study was to assess the impact of burosumab-twza on the symptom of osteomalacia through 48 weeks of treatment. The osteoid volume/bone volume score decreased from 26% at baseline to 11%. The osteoid thickness decreased from 17 mcm to 12 mcm. The mineralization lag time decreased from 594 days to 156 days.

There was also an open-label, quality of life study completed in 26 adults. Patients received low doses over the 4 month period: 0.05mg/kg at month 1, 0.1mg/kg at month 2, 0.3mg/kg at month 3 and 0.6mg/kg at month 4. Patient perception of chronic functional limitation significantly improved with burosumab-twza. The Medical Outcomes Study Short Form health Survey version 2 (SF-36v2) was assessed after 4 months of treatment. "Role Limitations due to Physical Health" improved significantly and by more than the minimal important change. The other components of the SF-36v2 and Western Ontario and McMaster Osteoarthritis Index (WOMAC) did not improve significantly.

Pediatric:

An open-label, randomized, parallel-group study was conducted in 26 patients from 5-12 years of age. Patients were randomized to receive burosumab-twza or placebo subcutaneous injections either every 2 weeks or every 4 weeks for a 16-week dose-titration followed by a 48-week treatment period. The primary endpoints were change from baseline to week 40 in severity of rickets as measured by total Thacher Rickets Severity Score (RSS) and change in from baseline to week 40 in the Radiographic Global Impression of Change (RGI-C) scale. The mean score on the RSS scale decreased from 1.9 at baseline to 0.8 at week 40 in the every 2 week dosing group and decreased from 1.7 at baseline to 1.1 at week 40 in the every 4 week dosing group ($p < 0.001$ for both groups compared to placebo). These reductions continued through week 64. The RGI-C scores suggested reduction in the severity of rickets for both treatment groups compared to placebo. Substantial healing of rickets was demonstrated in 54% of patients based on an RGI-C change from baseline ≥ 2.0 . The overall mean serum phosphorous level increased at week 40 (0.75 mg/dL) and at week 64 (0.84 mg/dL). Serum phosphorous levels within the normal range were reached by about half of the patients by week 6.

References

- [1] Product Information: Crysvisa subcutaneous injection, burosumab-twza subcutaneous injection. Ultragenyx Pharmaceutical Inc (per manufacturer), Novato, CA, 2018.
- [2] Micromedex® 2.0, (electronic version). Truven Health Analytics, Greenwood Village, Colorado, USA. Available at: <http://www.micromedexsolutions.com> (cited: 08/30/2018).
- [3] Carpenter TO, Whyte MP, Imel EA, et al. Burosumab Therapy in Children with X-linked Hypophosphatemia. N Eng J Med. 2018 May 24;378(21): 1987-1998
- [4] Ruppe MD, Zhang X, Imel EA, et al: Effect of four monthly doses of a human monoclonal anti-FGF23 antibody (KRN23) on quality of life in X-linked hypophosphatemia. Bone Rep 2016; 5:158-162.
- [5] <https://rarediseases.info.nih.gov/diseases/12943/x-linked-hypophosphatemia>

History

Date	Action and Summary of Changes
05.06.2019	New Policy